Neural Correlates of Stress and Favorite-Food Cue Exposure in Adolescents: A Functional Magnetic Resonance Imaging Study

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Abstract: Adolescence is a critical period of neurodevelopment for stress and appetitive processing, as well as a time of increased vulnerability to stress and engagement in risky behaviors. This study was conducted to examine brain activation patterns during stress and favorite-food-cue experiences relative to a neutral-relaxing condition in adolescents. Functional magnetic resonance imaging was employed using individualized script-driven guided imagery to compare brain responses with such experiences in 43 adolescents. Main effects of condition and gender were found, without a significant gender-by-condition interaction. Stress imagery, relative to neutral, was associated with activation in the caudate, thalamus, left hippocampus/parahippocampal gyrus, midbrain, left superior/middle temporal gyrus, and right posterior cerebellum. Appetitive imagery of favorite food was associated with caudate, thalamus, and midbrain activation compared with the neutral-relaxing condition. To understand neural correlates of anxiety and craving, subjective (self-reported) measures of stress-induced anxiety and favorite-food-cue-induced craving were correlated with brain activity during stress and appetitive food-cue conditions, respectively. High self-reported stress-induced anxiety was associated with hypoactivity in the striatum, thalamus, hippocampus, and midbrain. Self-reported favorite-food-cue-induced craving was associated with blunted activity in cortical-striatal regions, including the right dorsal and ventral striatum, medial prefrontal cortex, motor cortex, and left anterior cingulate cortex. These findings in adolescents indicate the activation of predominantly subcortical-striatal regions in the processing of stressful and appetitive experiences and link hypoactive striatal circuits to self-reported stress-induced anxiety and cue-induced favorite-food craving. *Hum Brain Mapp* 00:000–000, 2012.

Key words: stress; psychological; adolescence; motivation; appetite; fMRI

Additional Supporting Information may be found in the online version of this article.

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INTRODUCTION

Adolescence is a critical period of neurodevelopment for stress and appetitive processing [Somerville et al., 2010; Spear, 2009]. Adolescents are particularly vulnerable to immediate and long-term effects of stress, and, compared with children and adults, demonstrate more negative emotions and greater physiological responses to stress [Hyde et al., 2008; McCormick et al., 2010]. Stress has been associated with risky and addictive behaviors [Andersen and Teicher, 2009; Sinha and Li, 2007], especially with emotional and disordered eating among adolescents [Loth et al., 2008; Nguyen-Rodriguez et al., 2008]. In particular, disadvantaged youth frequently experience stressful life events, disrupted autonomic reactivity to stress, and poor health outcomes, including addiction [Cohen et al., 2010; Dobkin et al., 1998], obesity [Singh et al., 2010], and disordered eating [de Souza Ferreira and da Veiga, 2008].

Neural evidence from both human and preclinical literature suggests that cortico-striatal-limbic circuitry underlies both stress and pro-motivational (e.g., rewarding or appetitive) responses [Sinha and Li, 2007]. This circuit is comprised of two major systems, a prefrontal regulatory system and a limbic-striatal emotional center including the amygdala, striatum, and hippocampus [Davidson et al., 2000]. The balance between these two systems is thought to be critical to the development of stress- and reward-related behavior, and dysfunction in these areas has been associated with disordered eating, obesity, and addiction [Ernst and Fudge, 2009; Jastreboff et al., 2011b; Seo and Sinha, 2011]. In adolescents as compared with children or adults, an imbalance was found between the prefrontal regulatory and emotional striatal-limbic systems, which may help explain adolescent emotional and risk behavior [Somerville et al., 2010; Spear, 2009]. Previous work has found that adolescents show heightened amygdalar response to negatively valenced emotional faces and increased nucleus accumbens response to monetary reward [Somerville et al., 2010]. In addition, adolescents exhibit less prefrontal activation but greater activity in subcortical structures relative to adults in response to images of high-calorie foods [Killgore et al., 2003]. Anxiety symptoms in adolescents have also been associated with an imbalance between prefrontal cortical and amygdalar function [Hare et al., 2008]. Greater reliance on striatal-limbic regions during emotional processing in adolescents due to immature development of prefrontal regulatory system has been suggested to underlie their greater vulnerability to emotionally driven, risk-taking behaviors than individuals at other ages [Ernst and Fudge, 2009; Rutherford et al., 2010; Somerville et al., 2010; Spear, 2002].

Specifically, altered striatal activity has been reported during reward processing in adolescents, including hyperactive ventral striatal activity in response to reward [Ernst et al., 2005; Galvan et al., 2006] as well as hypoactive ventral striatum response in anticipation of reward [Bjork et al., 2004], especially in adolescents with risk-taking behaviors (e.g., substance abuse) [Schneider et al., 2012]. Reward-seeking behaviors such as drug addiction or overeating have also been proposed to result from a "reward deficiency syndrome" [Blum et al., 2000; Wang et al., 2001], such that striatal dopamine deficiency in obese individuals may predispose them to compensate for decreased striatal function by stimulating this region via compulsive eating [Wang et al., 2001]. It has been suggested that adolescents are similarly prone to have this sort of a "reward-deficiency syndrome" predisposing them to engage in addictive and impulsive/compulsive behaviors, especially under stressful situations [Spear, 2002].

Although prior research provides insight into neural patterns underlying motivational behaviors in adolescents, these studies typically used standard external stimuli (e.g., pictures, monetary reward). Thus, brain systems directly associated with personally relevant appetitive or stressful situations remain unclear. Research has also shown that there are individual differences in responses to different types of stressful and appetitive stimuli [Spreckelmeyer et al., 2009; Stroud et al., 2002], and personally relevant emotional experiences may recruit different brain networks from those with standard external stimuli [Gusnard et al., 2001; Ochsner et al., 2004]. These results emphasize a need to examine motivational neural system in the context of personally relevant situations. Moreover, studies have found that adolescents, as compared with adults, exhibit heightened physiological and neural responses to stressful and emotional stimuli [Somerville et al., 2010; Spear, 2009], suggesting that shared brain regions may contribute to the link between stress and reward-related risk behaviors. However, few studies in adolescents have concurrently examined neural responses to such stimuli and their relationships with emotional behaviors, such as anxiety and craving, within the same task paradigm.

Given the relevance of stress and eating problems to adolescent health, we investigated neural responses to stress and favorite-food cues while adolescents engaged in brief guided imagery of personally relevant situations. To effectively induce stress and appetitive experiences, we utilized a well-validated individually tailored imagery paradigm as previously described [for review see Sinha, 2009). We also examined the relationship between brain activations and subjective food craving and stress-induced anxiety during the food cue and stress conditions, respectively, considering the clinical relevance of these self-reported responses in the development of emotional disorders [Chaplin et al., 2008; Paliwal et al., 2008]. Based on previous research described earlier, we hypothesized that we would observe greater activity in subcortical regions, especially in striatal-limbic area, during stress and favorite-food-cue processing as compared with the neutral condition. We also expected to find that altered activity in striatal-limbic regions would be associated with high self-reported favorite food-cue-induced craving and stress-induced anxiety immediately following imagery sessions.

METHODS

Participants

Forty-three adolescents (16 girls, 27 boys) between the ages of 14–17 years (M = 15.58 years, SD = 0.78 years) participated. They were predominantly African American (93%) with a mean IQ of 93.2 (SD = 12.6, range = 71–116). Participants were fluent in English and free of significant medical or mental illness. Mental health was assessed by youth self-report using the National Institute of Mental Health Diagnostic Interview Schedule for Children (C-DISC-4.0-Y) [Shaffer et al., 2000]; no study participants met criteria for a current Axis I disorder, including substance abuse. Exclusion criteria included the use of psychotropic medications or medications potentially influencing autonomic responses, non-removable metal in one's body, claustrophobia, and inability to fit comfortably into the MRI scanner. We studied disadvantaged but otherwise healthy youth because there is a strong link between stress reactivity and disordered eating behaviors in this population, and these children seem at significant risk for stress-related negative health outcomes [Cohen et al., 2010; Nguyen-Rodriguez et al., 2008]. All participants were recruited from a larger cohort of children participating in a longitudinal study of disadvantaged youth [Mayes et al., 2005]. Members of this cohort were recruited at birth and followed every 6 months thereafter. Specifically, study participants were born into low-income families with low maternal educational attainment (approximately 20% of mothers reported less than a high school education and <3% had graduated college). Current life stress was assessed using the Negative Life Events Inventory (M=5.1, SD=3.12, range = 0–14) and the four-item Perceived Stress Scale (M=5.5, SD=2.83, range = 0–12). The Negative Life Events Inventory [Wills et al., 1992] is a 20-item self-report questionnaire that inquires whether certain stressful events occurred within the past year. The Perceived Stress Scale is a self-report questionnaire used to assess psychological stress in daily life (e.g., how stressful, unpredictable and overwhelming one perceives one's life to be) [Cohen et al., 1983]. The frequencies and types of negative events experienced by our study participants appear similar to those observed in other high-risk urban youth samples [Brady et al., 2009; Wills et al., 1996]. Girls and boys did not differ in age, race, IQ, or number of negative life events or perceived life stress.

Individualized Imagery Method and Script Development

The individually tailored imagery method, adapted from methods initially developed by Lang et al., has been extensively used in anxiety-disordered adults [Lang et al., 1980; McNeil et al., 1993]. It has also been used in numerous laboratory and brain imaging studies to induce emotion, stress, and craving [Cooney et al., 1997; Li et al., 2005; Sinha et al., 2009, 2011]. The utility of this method in other laboratory studies has also been demonstrated by successful elicitation of peripheral stress responses and drug craving responses predicting subsequent alcohol and drug relapse, and these findings provide external validity for this provocation technique [for reviews see Sinha et al., 2009, 2011].

Prior to the functional magnetic resonance imaging (fMRI) session, individualized scripts were generated via standardized, structured interview using Scene Development Questionnaires [Sinha, 2009] based on participants' experience of two stressful, two favorite-food, and two neutral-relaxing situations. For stress scripts, participants recounted highly stressful past-year situations and rated their distress levels on a 10-point Likert scale (1, not at all distressing; 10, the most stressful), and only situations rated =8 were accepted for script development. Examples of stressful situations included arguments with parents or peers, death or illness of loved ones, and tests or other difficulties at school. Favorite-food scripts were developed based on participants' choice of their favorite food; adolescents described recent times when they wanted, and ate their favorite food (e.g., pizza, fried chicken, ice cream). Neutral-relaxing scripts included situations like relaxing in one's room or sitting in a park. The style, content format, and length of scripts were standardized across conditions and participants based on previously described methods [Sinha, 2009]; and thus, each imagery trial only differs in individual stimulus (e.g., stress vs. neutral-relaxing). To decrease variability in individual imagery ability, all participants participated in a single relaxation and guided-imagery session prior to scanning [Seo et al., 2011; Sinha, 2009]. Stress scripts were rated for the type of stress as either: interpersonal (60%; personal violation, relationship, family conflicts, and betrayal), achievement (24.4%; school work, sports performance, and household role), medical (12.2%; injury and illness), or environmental (3.3%; housing and neighborhood). There was no difference in types of stressors reported by girls and boys.

Image Acquisition

A 3T Siemens Trio MRI system equipped with a standard quadrature head coil and employing a T2*-sensitive gradient-recalled single-shot echo-planar pulse sequence was used. Participants were offered the opportunity to acclimate to fMRI in a mock scanner prior to data collection. Anatomical images of the functional slice locations were obtained with spin echo imaging in the axial plane parallel to the anterior commissure - posterior commissure (AC-PC) line with repetition time (TR) = 300 ms, echo time (TE) = 2.46 ms, bandwidth = 310 Hz/pixel, flip angle = 60 degrees, field of view (FOV) = 220 × 220 mm, matrix = 256 × 256, 32 slices with slice thickness = 4 mm and no gap. Functional images were acquired with a single-shot gradient echo-planar-imaging sequence. Thirty-two axial slices parallel to the AC-PC line covering the whole brain

were acquired with TR = 2000 ms, TE = 25 ms, bandwidth = 2005 Hz/pixel, flip angle = 85 degrees, FOV = 220 × 220 mm, matrix = 64 × 64, 32 slices with slice thickness = 4 mm and no gap, 150 measurements. Following the completion of functional imaging, a high-resolution 3D Magnetization-Prepared-Rapid-Gradient-Echo (MPRAGE) sequence [TR = 2530 ms; TE = 3.34 ms; bandwidth = 180 Hz/pixel; flip angle = 7 degrees; slice thickness = 1mm; FOV = 256 × 256 mm; matrix = 256 × 256] was used to acquire sagittal images for multi-subject registration.

fMRI Trials

Six audio-taped imagery narratives (two trials per condition) were presented in a randomized counter-balanced fashion. Each trial was 5 min in duration, including a 1.5-min quiet baseline period followed by a 2.5-min imagery period and a 1-min quiet recovery period. To directly evaluate in-scan emotional experience, participants were asked to rate their anxiety and food craving on a 0–10 scale (0, not at all; 10, more than ever) before and immediately after each fMRI trial. Anxiety rating refers to how "tense, anxious and/or jittery" participants felt at the moment. For favorite food craving, participants were instructed, "Imagine you have "_____" [subject's favorite food described in narrative script (e.g., pizza)] in front of you right now," and asked, "On a scale of 0–10, how much do you want [favorite food] right now?" To mitigate the influence of emotional states induced during the preceding trial, participants participated in a 2-minute, progressive relaxation following each trial, and the next trial was not initiated until anxiety and craving ratings were at the previous trial's baseline level.

fMRI Analysis

All data were converted from Digital Imaging and Communication in Medicine (DICOM) format to analyze format using XMedCon [Nolf, 2003]. To allow the signal to achieve steady-state equilibrium between radio frequency pulsing and relaxation, the first 10 images at the beginning of each of the six functional series were discarded during the conversion process, leaving 140 measurements for analysis. Images were motion corrected using SPM5 for three translational and three rotational directions [Friston et al., 1996]. Trials with linear motion in excess of 1.5 mm or rotation greater than 2 degrees were discarded. Individual subject data were analyzed using a General Linear Model on each voxel in the entire brain volume with a regressor specific for the task. The regressor was the block of time while the participants were listening to the particular script (as compared with the baseline resting period). Temporal filtering was performed by including drift correction in the General Linear Model, and drift regressors were used to remove the mean time course, linear trend, quadratic trend, and cubic trend for each run. The resulting functional images were averaged according to script type and spatially smoothed with a 6-mm Gaussian kernel. The output maps were normalized beta-maps, in the acquired space (3.44 mm × 3.44 mm × 4 mm).

To bring the data into a common reference space, three registrations were applied to the individual normalized beta-maps using BioImage Suite software (http://www.bioimagesuite.org/) [Duncan et al., 2004]. First, linear registration was performed to register each subject's raw functional images with that subject's 2D anatomical images, and then again to register these 2D images with the individual's 3D anatomical image. A non-linear registration was then computed between the individual 3D anatomical image and a reference 3D image, the Colin27 Brain [Holmes et al., 1998], in Montreal Neurological Institute (MNI) space.

For second-level group analysis using random mixed-effects models, data were converted to AFNI format (http://afni.nimh.nih.gov) [Cox, 1996] and later returned to ANALYZE format for viewing in BioImage Suite. Effects of condition and gender were examined in AFNI Matlab library in a 2-way ANOVA in which subject was treated as a random factor. Using Monte Carlo simulations conducted with AlphaSim in AFNI, a family-wise error (FWE) rate correction was applied to correct for multiple comparisons [Cox, 1996; Seo et al., 2011; Xiong et al., 1995]. To assess the source of resulting significant effects, whole-brain, condition-specific contrasts and gender contrasts were conducted. Whole-brain correlational analyses, in which individual activation patterns were correlated with self-report post-imagery ratings of anxiety in the stress condition and food craving in the favorite-food condition, were examined using BioImageSuite with application of FWE correction for multiple comparisons. Correlations were applied to the group fMRI data to examine individual difference (between-subject variability) in brain activity associated with anxiety and craving response.

RESULTS

Behavioral Responses to Stress and Favorite-Food fMRI Trials

Self-report ratings (range 0–10) of anxiety and favorite-food craving collected before and immediately after each scan trial indicated significant increases in anxiety following the stress condition and in favorite-food craving following the favorite-food-cue condition, but no significant changes in either measure during the neutral-relaxing condition. In response to stress imagery, adolescents demonstrated significant increases in self-reported anxiety (t = 3.6, $P < 0.001$; pre-imagery: $M = 3.26$, SD = 2.38; post-imagery: $M = 3.97$, SD = 2.54). In response to food imagery, elevated self-reported food craving ($t = 4.2$, $P < 0.0001$) was observed (pre-imagery: $M = 5.18$, SD = 3.08; post-

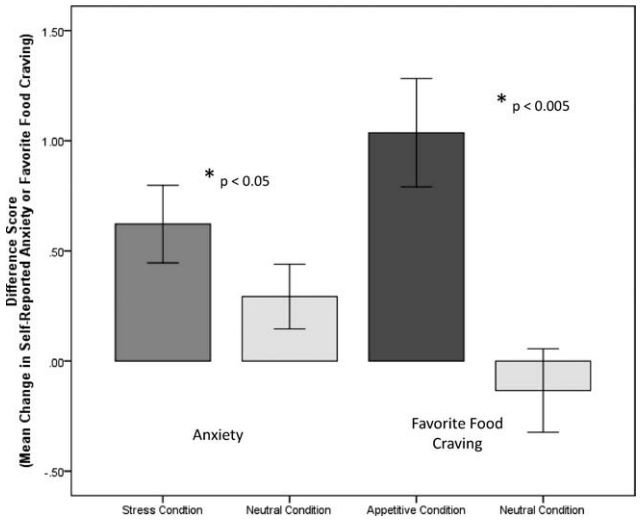

Figure 1.

Comparison of changes in self-reported anxiety and favorite food craving before and after stress, appetitive, and neutral imagery conditions. Relative to neutral-relaxing scripts, stress scripts induced significantly greater increases in self-reported anxiety ($t = 2.02$, $P < 0.05$), and favorite-food scripts induced significantly greater increases in self-reported food craving ($t = 3.05$, $P < 0.005$). Error bar indicates standard error of the mean.

imagery: $M = 6.18$, SD $= 2.99$). Relative to neutral-relaxing scripts, stress scripts induced significantly greater increases in self-reported anxiety ($t = 2.02$, $P < 0.05$), and favorite-food scripts induced significantly greater increases in self-reported food craving ($t = 3.05$, $P < 0.005$, see Fig. 1). Average ratings of anxiety and food craving did not differ between boys and girls. These results indicate successful experimental induction of stressful and favorite-food-related emotional/motivational states in our sample.

Brain Responses to Stress and Favorite-Food Imagery Trials

Whole-brain-corrected analyses revealed significant main effects of both condition and gender (each at $P < 0.05$, two-tailed, FWE-whole-brain-corrected), but no significant interactions (Tables I and II, Fig. 2). Main effects of condition (stress, favorite-food, and neutral-relaxing) were seen in predominantly subcortical regions including the thalamus, striatum, insula, hippocampus, midbrain, and posterior cerebellum, as well as cortical areas including the anterior cingulate (BA 24/32), medial frontal gyrus (BA 6), and superior and middle temporal gyri (BA 21/22/38; Fig. 2). During the stress condition as compared with the neutral-relaxing condition, participants showed greater activation in the striatum, thalamus, left hippocampus and parahippocampal gyrus, left superior and middle temporal gyri, bilateral midbrain [including substantia nigra and periaqueductal gray (PAG)] and right cerebellum, and decreased activation in right pre- and post-central gyri and inferior parietal lobule. The contrast of the favorite-food condition versus the neutral-relaxing condition demonstrated increased activation in the striatum, thalamus, and midbrain, and decreased activation in the anterior cingulate cortex, posterior/middle insula, superior medial gyrus, and superior and middle temporal gyri. During the stress condition relative to the favorite-food one, greater temporal lobe activation was observed bilaterally (left: 6021 mm^3, $t = 2.2$, $X = -48$, $Y = -45$, $Z = 8$; right: 6897 mm^3, $t = 2.4$, $X = 47$, $Y = -4$, $Z = -17$). There was no brain region showing greater activity in the favorite-food relative to stress condition contrast. A main effect of gender identified activation differences predominantly in cortical regions including the superior, middle, and medial frontal gyri, as well as bilateral parietal lobes ($P < 0.05$ two-tailed, FWE-corrected), with greater activation in boys than girls (see Supporting Information Table 1 and Fig. 1).

Correlations Between Brain Activation and Subjective Ratings

Whole-brain, voxel-based correlational analyses indicated significant associations between task-related brain activity and subjective measures of post-imagery, favorite-food-cue-induced craving, and stress-induced anxiety (Table III, Fig. 3; Supporting Information Figs. 2 and 3).

Favorite-food-cue craving was inversely correlated with brain activation during favorite food-cue exposure at $P < 0.05$, two-tailed, FWE-corrected (Supporting Information Fig. 3). Given the strength and breadth of the correlations, we report findings using a more stringent threshold ($P < 0.01$, two-tailed, FWE-corrected; Table III, Fig. 3). Brain regions negatively correlated with favorite-food-cue-induced craving at the $P < 0.01$ threshold included the right ventral and dorsal striatum, left anterior cingulate cortex, pre/supplementary motor cortex, and medial frontal gyrus. Stress-induced anxiety correlated inversely with activation during stress exposure in the thalamus, caudate, midbrain (PAG), and right hippocampus ($P < 0.05$, two-tailed, FWE-corrected; Supporting Information Fig. 2).

DISCUSSION

The purpose of our study was to examine neural patterns underlying responses to individualized stressful and favorite-food cues in adolescents. We found that adolescents demonstrate striatal-thalamic activation to stress and favorite-food cues, suggesting that they rely largely on subcortical regions in stress and favorite-food-cue processing. This study using personally relevant stimuli is consistent with previous findings of striatum-dependent reward processing (including to food cues) in adolescents and revealed that adolescents also utilize striatal-thalamic

TABLE I. Condition main effects

Regions of Activation	Lat	BA	Coordinates			Volume (mm^3)	F
			X	Y	Z		
Medial frontal gyrus	B	6	2	−6	53	2181	4.24
Anterior/middle cingulate gyrus	B	24, 32	0	−2	44	5548	4.65
Posterior/middle insula	R	13	41	8	0	1091	3.78
Thalamus	B	—	−4	−12	9	6457	4.61
Caudate	L	—	−14	−1	15	1810	5.45
	R	—	18	−11	21	983	4.61
Hippocampus	L	—	−20	−14	−14	112	3.52
Midbrain	B	—	−2	−23	−9	5296	4.56
Substantia nigra, periaqueductal gray	L	—	−10	−19	−12	207	2.88
Substantia nigra, periaqueductal gray	R	—	11	−18	−12	147	2.31
Superior/middle temporal gyrus	L	21, 22	−57	−31	−4	7177	3.99
	R	21, 22, 38	46	−1	−11	5227	4.02
Cerebellum, posterior lobe	R	—	22	−72	−23	7232	4.62

Significant activations at $P < 0.05$ (two tailed, whole-brain FWE corrected). Montreal Neurologic Institute (MNI) coordinates were used.
Lat, laterality; B, bilateral; L, left; R, right; BA, Brodmann's area.

TABLE II. Neural activations during stress and favorite-food cue exposures

Regions of activation	Lat	BA	Coordinates			Volume (mm^3)	t	Coordinates			Volume (mm^3)	t
			X	Y	Z			X	Y	Z		
			Stress cue > neutral					Food cue > neutral				
Caudate	L	—	−14	−1	16	2003	2.9	−12	−1	15	1331	2.53
	R	—	17	−8	20	1231	2.7	11	1	11	242	2.16
Thalamus	B	—	−3	−12	7	10,155	2.73	−6	17	8	2479	2.32
Hippocampus	L	—	−21	−14	−15	158	2.24	—	—	—	—	—
Parahippocampal gyrus	L	—	−18	−24	−12	337	2.53	—	—	—	—	—
Midbrain	B	—	−1	−23	−12	6329	2.61	−1	27	−8	1721	2.4
Substantia nigra, periaqueductal gray	L	—	−10	−19	−11	213	2.83	—	—	—	—	—
Substantia nigra, periaqueductal gray	R	—	10	−18	−12	209	2.35	—	—	—	—	—
Superior/middle temporal gyrus	L	21, 22	−58	−30	−5	11,907	2.49	—	—	—	—	—
Cerebellum	R	—	22	−73	−32	10,923	2.66	—	—	—	—	—
			Stress cue < neutral					Food cue < neutral				
Superior medial gyrus (motor cortex)	B	6	—	—	—	—	—	1	−9	56	3720	−2.43
Anterior cingulate cortex	B	24, 32	—	—	—	—	—	0	0	41	8367	−2.7
Posterior/middle insula	L	13	—	—	—	—	—	−41	0	3	2465	−2.35
	R	13	—	—	—	—	—	42	2	0	4466	−2.36
Superior/middle temporal gyrus	L	22, 38	—	—	—	—	—	−51	−1	−1	1377	−2.39
	R	22, 38	—	—	—	—	—	51	0	−8	4693	−4
Pre-/post-central gyrus (sensory cortex)	R	2, 3, 4	50	−23	49	6831	−2.5	—	—	—	—	—
Inferior parietal lobe	R	40	58	−27	33	1260	−2.27	—	—	—	—	—

Significant activations at $P < 0.05$ (two-tailed, whole-brain FWE corrected). MNI coordinates were used.
Lat, laterality; B, bilateral; L, left; R, right; BA, Brodmann's area.

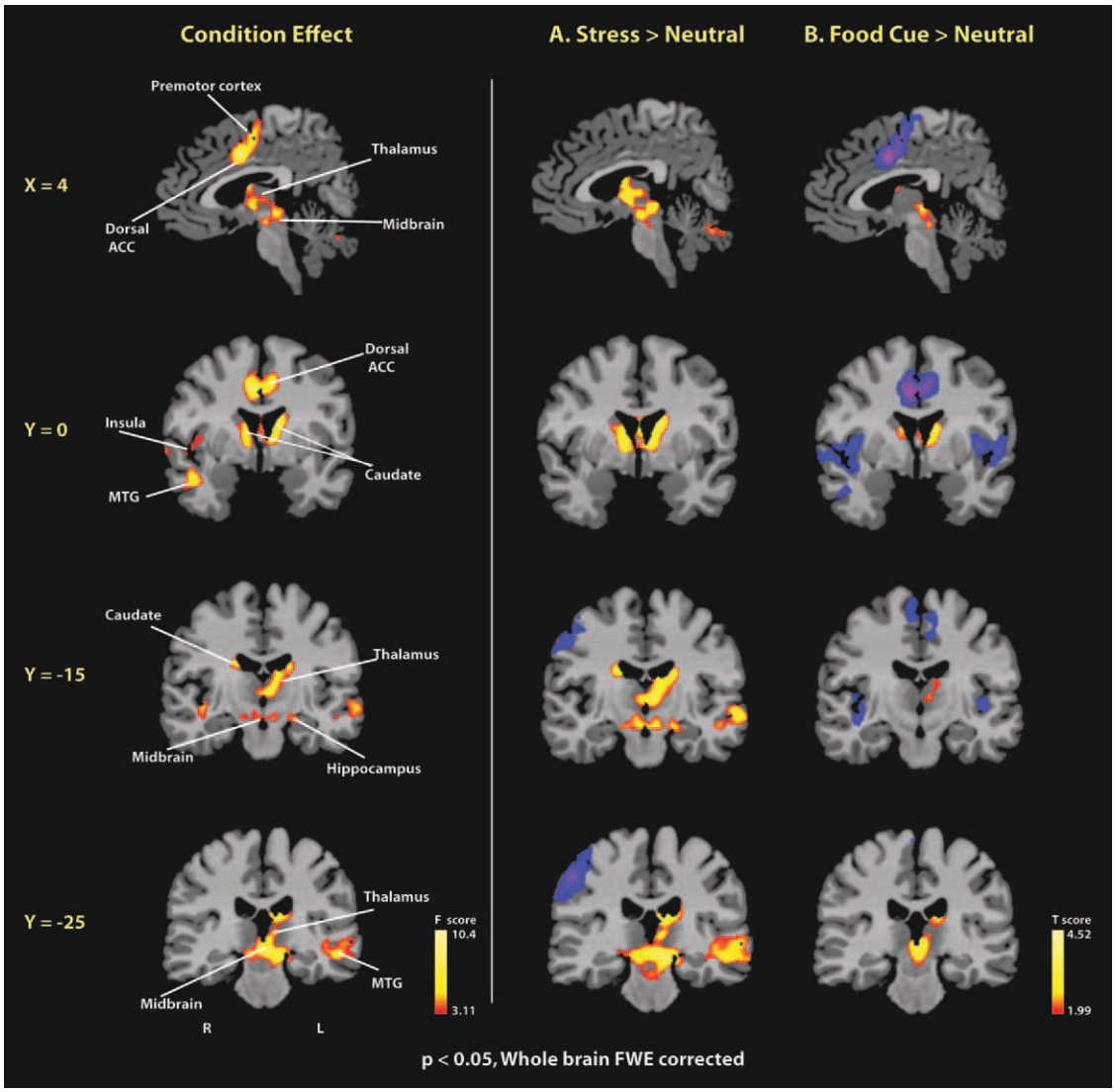

Figure 2.

Main effects of condition and pair-wise comparisons illustrating the source of the main effects. Common brain regions activated during both stress and favorite-food-cue conditions relative to the neutral-relaxing condition include activations of the caudate, thalamus, and midbrain. For the stress relative to neutral-relaxing condition contrast, brain regions additionally activated included the medial temporal gyrus and hippocampus. For the favorite-food-cue relative to neutral-relaxing condition contrast, decreased activity was observed in the pre-motor cortex, dorsal anterior cingulate cortex, insula and temporal lobe. See Tables I and II for locations and extents of regional activations. Analyses were thresholded at $P < 0.05$ two-tailed, whole-brain FWE-corrected. All coordinates are given in MNI space. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

regions during stress processing. Despite some differences (e.g., in temporal lobe activation), there was substantial overlap between brain regions underlying stress and favorite-food-cue processing, suggesting shared circuitry in these two processes in adolescents. Interestingly, high self-reported favorite-food-cue-induced craving and stress-induced anxiety responses associated with decreased activity in striatal and thalamic regions, suggesting that hypoactivity in striatal-thalamic regions may underlie risk-taking behaviors associated with stress and favorite-food-cues in adolescents. Implications of these findings are discussed later.

Adolescent Neural Circuits of Stress and Favorite-Food Cue Processing

During favorite-food-cue relative to neutral-relaxing conditions, activation was observed in striatal-thalamic and

TABLE III. Neural correlates of self-reported favorite food craving

Regions of activation	Lat	BA	Coordinates			Volume (mm^3)	r
			X	Y	Z		
Favorite-food-cue-induced craving							
Striatum (caudate, putamen)	R	—	20	13	−3	1347	−0.5
Anterior cingulate gyrus/SFG/MFG	L	10, 32	−13	39	16	1321	−0.55
Middle cingulate gyrus/MFG	B	6, 32	−1	−12	44	4511	−0.56

Significant correlations at $P < 0.01$ (two-tailed, whole-brain FWE corrected). Lat, laterality; B, bilateral; L, left; R, right; BA, Brodmann's area. MNI coordinates were used.
SFG, superior frontal gyrus; MFG, medial frontal gyrus.

other subcortical regions including the caudate, thalamus, and midbrain, and decreased activity was observed in cortical regions including the posterior/middle insula and anterior cingulate, temporal, and motor cortices. In adults, striatal-thalamic regions underlie responses to a range of positive experiences, with striatal-thalamic activation observed in studies of the neural processing of monetary rewards [Rademacher et al., 2010], social drinking [Seo et al., 2011], and palatable foods [Schur et al., 2009]. The anterior cingulate and motor cortices participate in the monitoring and regulation of responses to appetitive stimuli [Haber and Knutson, 2010]. Deactivation in these cortical regions during food-cue, relative to neutral trials, suggests adolescent vulnerability to reward regulation. Consistent with this, we found decreased activity in these areas are associated with high food craving, suggesting

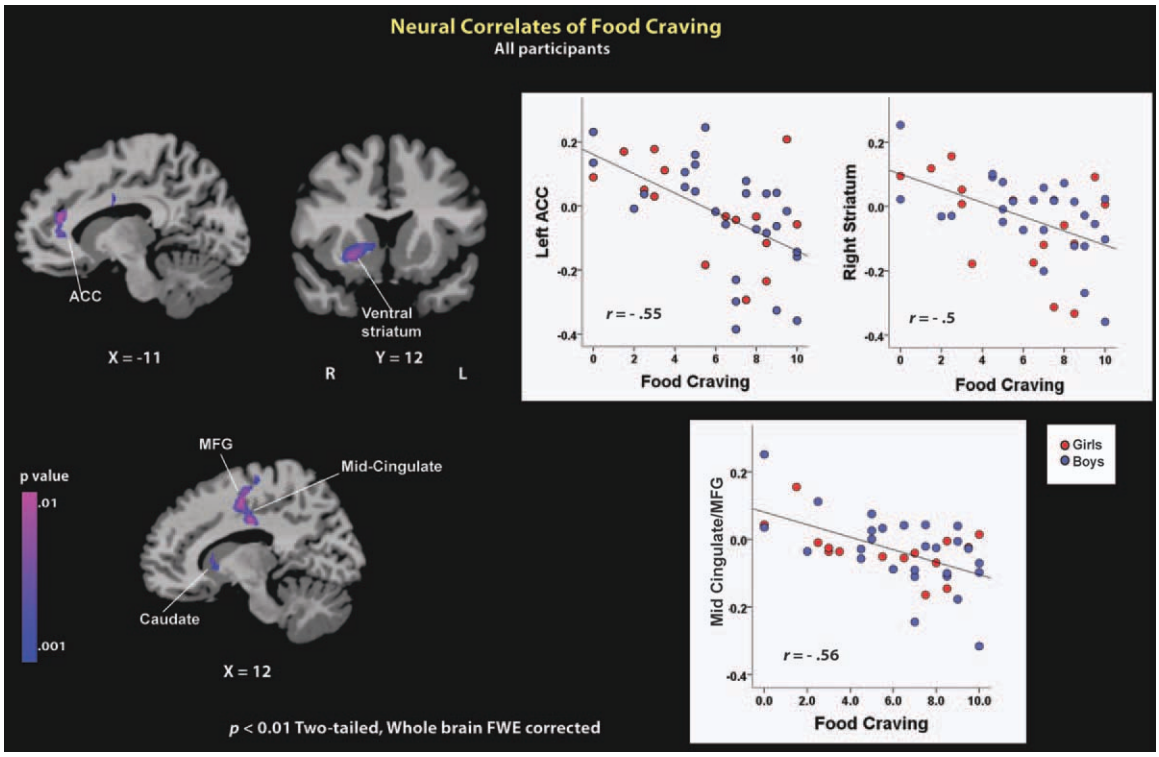

Figure 3.

Correlations depicting neural correlations between subjective measures of cue-induced favorite-food craving and regional activations during the favorite-food-cue condition. Blue and purple voxels indicate negative correlations observed between self-reported favorite-food craving and activity in the left anterior cingulate cortex, right ventral and dorsal striatum, medial frontal gyrus and mid-cingulate gyrus. Corresponding scatterplots are shown for these regions. See Table III for locations and extents of regional correlations. Analyses were thresholded at $P < 0.01$, two-tailed, whole-brain FWE-corrected. L, left; R, right; ACC, anterior cingulate cortex; MFG, medial frontal gyrus. All coordinates are given in MNI space. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

that difficulties in reward modulation may contribute to high food craving in adolescents. Therefore, our observation of increased subcortical striatal activity with decreased cortical activity suggests that favorite-food imagery may preferentially activate subcortical regions considered important in promoting motivated behaviors in the absence of cortical activations involved in modulation of appetitive responses and behavioral control, consistent with adolescent brain and behavior developmental models [Somerville et al., 2010].

In our adolescent sample, stress exposure relative to a neutral-relaxing condition also activated striatal-thalamic-midbrain and other subcortical regions, including the caudate, thalamus, hippocampus, substantia nigra and PAG, and cerebellum, and also activated the temporal lobe. These regions have previously been reported to be involved in stress and aversive emotional processing in adults. Dorsal striatum (caudate) activation contributes importantly to stress processing, and chronic stress may influence decision-making via modulation of frontostriatal pathways [Dias-Ferreira et al., 2009; Seo et al., 2011]. The hippocampus and PAG are involved in basic emotional arousal including stress and anxiety/fear [Fanselow and Dong, 2010; Keay and Bandler, 2001]. Neural circuits connecting the hippocampus, temporal cortex, striatum, thalamus, midbrain, and cerebellum link arousal and the processing of emotionally salient material and memories [Lane et al., 1997; Svoboda et al., 2006]. In addition, greater limbic-striatal activation to cue-based aversive or distressing stimuli, such as viewing fearful faces or registering the omission of an expected monetary reward, has been observed in adolescents [Somerville et al., 2010]. Our current findings of the neural correlates of stress processing are consistent with and extend those from previous studies by showing additional evidence of the role of these subcortical regions in experiencing personally relevant stressful situations.

In addition, hypoactivity in cortical areas, including the sensory cortex and inferior parietal lobe, was evident during stress exposure relative to neutral trials. The inferior parietal lobe is involved in adaptive responses requiring sensory-motor integration and oculomotor control [Clower et al., 2001; Lynch, 1980]. Stress is a state of disrupted homeostasis in adaptive sensory and physiological responses to emotional challenges [Sinha, 2008]. Thus, hypoactivation in sensory and inferior parietal cortices could reflect disrupted sensory modulation during stressful states in adolescents.

We did not observe significant prefrontal activation in our sample during stress or favorite-food cue processing. This is contrary to adult neuroimaging studies that have found both subcortical and prefrontal activation in stress and appetitive processing [Jastreboff et al., 2011a; Pelchat et al., 2004; Schur et al., 2009; Sinha and Li, 2007]. In a study utilizing a similar imagery paradigm among adults, stress and appetitive processing, as compared with neutral imagery, elicited activation of the prefrontal regulatory system as well as striatal-thalamic regions [Seo et al., 2011; Sinha and Li, 2007]. The prefrontal cortex has been implicated in the regulation of emotionally driven behaviors in subcortical structures [Goldin et al., 2008]. PFC hypoactivity, or the absence of prefrontal cortical activation may reflect a lack of a cognitive awareness of underlying anxieties or appetites, leading to decreased cortical regulation and disinhibited activity in the subcortical circuitry [Mayberg, 2003]. The absence of activation of the prefrontal control system in our study suggests that adolescents engage emotion-linked subcortical circuits rather than prefrontal regulatory regions in responses to stressful and appetitive stimuli, a pattern which may reflect either limited adolescent self-awareness of anxiety and craving or functional immaturity. Structural developmental studies suggest that striatal-limbic regions reach maturity before the prefrontal cortex [for review, see Gogtay and Thompson, 2010] and other functional neuroimaging studies have found that adolescents rely more heavily on striatal-limbic than prefrontal cortical circuits for emotional and motivational processing [for review, see Somerville et al., 2010]. Such heightened activity of striatal motivational circuits in conjunction with relatively immature prefrontal cortical function has been proposed to underlie adolescent propensity to engage in reward-oriented risk-taking behaviors [Spear, 2009], and our finding that stressful and appetitive stimuli engage similar subcortical regions in the absence of prefrontal modulatory activity further supports this theory. However, our data should be interpreted with caution, because we did not directly compare the brain responses of adolescents to adults. Future studies directly comparing these adolescent and adult populations are needed to fully elucidate developmental patterns during stress and appetitive emotional processing and understand adolescent specific risk-taking and reward-seeking behaviors.

Subjective Measures of Craving and Anxiety and Striatal Hypoactivity

Adolescents with subjective reports of high favorite-food-cue-induced craving displayed decreased activity in cortico-striatal circuits, whereas those with subjective reports of high stress-induced anxiety showed hypoactivity in striatal-thalamic regions. More specifically, self-reported favorite-food-cue-induced craving measures inversely correlated with activity in cortical-striatal regions, including in the medial prefrontal, motor, and left anterior cingulate cortices and right dorsal and ventral striatum. In adults, the striatum contributes importantly to inhibitory motor control and motivated behaviors [Vink et al., 2005], with the ventral striatum linking the limbic and motor systems, modulating motivated behaviors and contributing to addictions [Haber and Knutson, 2010]. Low striatal response to highly palatable food has been linked to obesity [Stice et al., 2008], consistent with

patterns of striatal hypofunction observed in individuals with other substance or nonsubstance addictions [Frascella et al., 2010]. Addiction theory suggests that substance abusers may have a reward deficiency syndrome and that blunted striatal function may drive reward-seeking behavior, leading individuals to seek greater stimulation to activate these regions [Bjork et al., 2004; Blum et al., 2000]. Consistent with this theory, we found that hypoactivity in the striatum is associated with high self-reported favorite-food-cue-induced craving. The striatum closely interacts with regulatory regions including medial prefrontal, anterior cingulate, and motor cortices to effectively modulate motor-control and approach behavior to reward stimuli [Haber and Knutson, 2010]. Decreased activity in cortico-striatal regions in association with stronger subjective desires for food suggests that hypofunction of reward modulation circuitry may underlie excessive eating-related behavior and potentially other motivated behaviors with addictive potentials.

High stress-induced anxiety was associated with less activity mainly in the thalamus but also in the striatum (caudate), midbrain (PAG), and hippocampus. The thalamus is the primary relay region of sensory information to the cortex and decreased thalamic activity is associated with reduced sensory inputs to the cortex [Castro-Alamancos, 2002]. Deficient white matter integrity in anterior thalamic radiations has been observed in patients with mood disorders [Sui et al., 2011] and improvement in mood and anxiety was associated with increased thalamic function [Streeter et al., 2010]. In our study, striatal hypoactivity was associated with high self-reported stress-induced anxiety and favorite-food-cue-induced craving. As decreased striatal activity has also been associated with impaired inhibition of impulsive behaviors [Vink et al., 2005], striatal hypoactivity may underlie drives to engage in compensatory stress- and reward-related eating or risk-taking behaviors, perhaps to enhance striatal stimulation [Bjork et al., 2004]. A recent study of social exclusion also found that adolescents not only demonstrated striatal activity in response to social exclusion, but also that this striatal activity was negatively correlated with subjective distress [Masten et al., 2009]. In conjunction with our findings, these results suggest that the thalamo-striatal regions may play a modulatory role in aversive and appetitive emotional processing during adolescence prior to the maturation of prefrontal regulatory circuits, and that hypoactivity in these regions may underlie engagement in maladaptive behaviors associated with stress and favorite-food cues in adolescents.

Limitations and Conclusions

In summary, this study elucidated patterns of striatal-thalamic activation associated with stress and favorite-food-cue processing and identified an inverse correlation between striatal-thalamic activations and subjective measures of stress-induced anxiety and favorite-food-cue-induced craving in adolescents. We did not observe any correlation between self-report ratings and patterns of brain activation during neutral scripts (which served as our baseline condition), thus it is unlikely that providing self report ratings significantly influenced brain response attributed to the task itself. The extent to which the patterns observed may be more pronounced in disadvantaged youth and related to their risky choices and poor health outcomes, such as anxiety, emotional eating, and other stress-related disorders, require direct investigation [Taylor et al., 2006]. Studying disadvantaged youth of minority racial status has both advantages and limitations. Studying emotional behaviors in this population is important because they typically experience high stress-related risk. However, it is not known if these findings generalize to other groups of adolescents. Additional limitations include a numerically limited (albeit statistically significant) change in self-reported anxiety in response to stress exposure, the absence of "food-liking" measures to assess individual differences in appetitive salience, and a narrow age range in our sample (age 14–17 years). Although this last feature has advantages of creating a more homogenous sample, a broader age range could allow for examination of developmental differences between younger and older teens. The study also lacked structured assessments of overeating behaviors and future studies that include overeating measures may help understand brain systems associated with disordered eating in adolescents. Additionally, future studies involving larger samples could assess for differences related to specific types of stressors. Despite these limitations, this study is the first to demonstrate specific cortico-striatal-thalamic brain activations associated with personally relevant stress and favorite-food cues in adolescents and relate them to their subjective self-reported responses of anxiety and craving, respectively. These findings provide a framework for future studies examining how interventions related to stress reduction might help alter neural function and limit engagement in risk behaviors including maladaptive patterns of food consumption.

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